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제 2형 유두신장암의 유전분석을 통한 치료 전략 모색

Treatment Strategy for Papillary Renal Cell Carcinoma Type II based on Genetic Analysis

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Abstract

Introduction: Papillary renal cell carcinoma type 2 (PRCC2) is refractory to systemic treatment and has a dismal prognosis compared with clear cell renal cell carcinoma (ccRCC). In our previous study, PRCC2 had high PBRM1 expression and suggested that poor prognosis. Previous genetic studies showed that genetic alterations in PRCC2 were heterogeneous regardless of germline or somatic mutations. In this study, we aimed to perform precision treatment of PRCC2 based on genetic information.

Methods: We performed exome and genome sequencing of tumor tissues and matched normal samples. Based on sequencing data, we treated patients with metastatic PRCC2 using precision oncology.

Results: Four patients underwent curative surgery of PRCC2 and three patients had metastatic PRCC2. All PRCC2 heterogeneously harbored own driver mutations. Two out of the three patients with metastatic disease had fumarate hydratase (*FH*) germline mutations. One patient with a germline

FH mutation was diagnosed with hereditary leiomyomatosis renal cell carcinoma. He was treated with bevacizumab and erlotinib combination and showed a durable response. The other metastatic PRCC2 patient harboring a germline *FH* mutation had an additional somatic *FH* mutation and was durably controlled with pazopanib. Other metastatic PRCC2 patient with somatic *PBRM1* and *SETD2* mutations had over 5 years of overall survival with axitinib treatment.

Conclusions: We performed precision systemic treatment based on genetic information. Genome sequencing could help identify candidates for targeted therapy in PRCC2, a genetically heterogeneous disease.

Keywords: Papillary renal cell carcinoma type 2; Comprehensive analysis; Next-generation sequencing; Precision Oncology

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LIST OF ABBREVIATIONS

PRCC2: Papillary renal cell carcinoma type 2

FH: Fumarate hydratase

RCC: Renal cell carcinoma

PRCC: Papillary renal cell carcinoma

HLRCC: Hereditary leiomyomatosis and renal cell carcinoma

HIF1a: Hypoxia inducible factor 1-alpha

ARE: Antioxidant response element

BWA: Burrows-Wheeler Alignment

SNV: Single nucleotide variants

Indels: Insertions and deletions

ACMG: American College of Medical Genomics and Genetics

AF: Allele frequency

CNA: Copy-number alterations

SV: Structural variation

TKI: Tyrosine kinase inhibitor

VEGFR: Vascular endothelial growth factor-receptor

EGFR: Epithelial growth factor receptor

TCA: Tricarboxylic acid cycle

GLUT: Glucose transporter

VHL: von Hippel-Lindau

MMR: Mismatch repair

Introduction

Renal cell carcinoma (RCC) is a heterogeneous disease comprising a number of different types of cancer (1, 2). The genetic background differs among various forms of RCC, and treatment response and prognosis vary according to subtype (3-6).

Previously, RCC is categorized into four subtypes according to histologic criteria. The most prevalent form, clear cell RCC, accounts for 75% of the cases, papillary renal cell carcinoma (PRCC) accounts 15-20%, chromophobe for 5% and oncocytoma for 5%. PRCC is divided into type 1 and type 2 (7). In clinicopathologic characteristics, type 1 disease has scant pale cytoplasm and low-grade nuclei and type 2 disease of abundant eosinophilic cytoplasma and large nuclei. In terms of clinical prognosis, type 1 disease has a relatively good prognosis compared to type 2 (1). Genetic alterations also differ between type 1 and type 2 PRCC (7-9). In particular, type 1 PRCC frequently harbors *MET* alteration regardless of sporadic or hereditary disease (7).

PRCC type 2 (PRCC2) comprises a number of different types of non-PRCC type 1 cancers, including hereditary leiomyomatosis and renal cell carcinoma (HLRCC) (10). HLRCC is the most aggressive subtype of

PRCC and harbors germline pathologic variants of fumarate hydratase (*FH*), which encodes one of the Krebs cycle enzymes (11). A pathologic variant associated with loss of function of FH leads to stabilization of hypoxia inducible factor 1-alpha (HIF1a) and facilitates the metabolic shift to aerobic glycolysis for ATP production. Therefore, HLRCC takes advantage of neo-angiogenesis, and an anti-angiogenesis approach is the key mechanism underlying systemic therapy for HLRCC (8, 12). In addition, other genetic alteration, *TFE3* translocation was reported in RCC in children and young adults and was associated with a grave prognosis (13). Recent our study also presented that PRCC2 had grave prognosis with PBRM1 expression (14).

There has been a steady effort to find genetic alterations of PRCCs. Exome and genome sequencing data suggest that the driver genetic alterations of PRCCs are varied, and somatic copy number alterations might be pathogenic events during the genetic evolution of PRCCs (15). Furthermore, large-scale genomic characterization of PRCC demonstrated that PRCC2 is divided into three subgroups according to genetic alterations. *CDKN2A* silencing, *SETD2* mutation, *TFE3* fusion, and NRF2-antioxidant response element (ARE) pathway activation were found in PRCC2 including *FH* mutation (7). Moreover, these genetic alterations are significantly related to cancer prognosis.

In this study, we performed exome and genome sequencing of PRCC2 patient samples to characterize their genomic landscapes. Potentially functional rare germline mutations in a wide range of known cancer genes as well as somatic mutations of a few papillary renal cell carcinoma-related genes such as *ALK*, *CSF1R*, *NF2*, *SETD2*, and *FH* were identified from our sequencing analysis. We also found previously reported recurrent copy gains of chr7, chr16, and chr17 in papillary renal cell carcinoma from our data as well. Our analysis confirmed the heterogeneous nature of PRCC2 genomic characteristics and identified genetic biomarkers for the prediction of prognosis and drug response in PRCC2.

Materials and Methods

Patients and sample preparation

We performed genetic analysis of PRCC2 using prospectively collected, surgically removed, fresh frozen samples of renal cell carcinoma and paired normal tissues in the Seoul National University Hospital tissue bank. Two other formalin-fixed paraffin-embedded samples from patients with metastatic PRCC2 were also included. These seven samples were reviewed by qualified pathologists and histologically classified as PRCC2.

Genomic DNA was extracted from FFPE samples using a QIAgen FFPE Tissue DNA kit. DNA and RNA were extracted from the fresh frozen samples using GeneAll exgene cell SV kit and Ambio PureLink RNA mini kit, respectively. Concentrations of DNA and RNA were measured using Qubit.

Exome capture, library construction and sequencing

Up to 3 μg of genomic DNA was sheared with a Covaris SS Ultrasonicator and adaptors were then ligated to both ends of the fragments.

Adaptor-ligated templates were purified using Agencourt AMPure SPRI beads, and fragments with an insert size of ~200 bp were isolated. Exons were captured from adaptor-ligated DNAs using SureSelect Human All Exon v4+UTRs kit (71Mb) according to the manufacturer's instructions (Agilent Technologies). PCR amplification of the libraries was carried out for four cycles in the pre-capture step and for ten cycles after capture. Paired-end sequencing, resulting in sequences of 101 base pairs from each end of the fragments, was performed on the HiSeq 2000 platform (Illumina) following the manufacturer's instructions. Image analysis and base calling were performed using the Illumina pipeline with default settings.

Bioinformatics analysis

Whole-genome sequencing analysis was performed for the five pairs of PRCC2 and matched control samples (four adjacent normal tissues and one blood sample). Whole-exome sequencing analysis was conducted for the two pairs of PRCC2. Reads were mapped to human reference genome (hg19) using Burrows-Wheeler Alignment (BWA) tool 0.7.12 (16). The mapped reads were processed using GATK best practice pipeline (Table 2) (17). We used the Mutect2 (version 3.6)(18) and GATK HaplotypeCaller (version 3.6)

algorithms in order to identify somatic and germline single nucleotide variants (SNVs)/short insertions and deletions (indels). Germline variants were categorized by the American College of Medical Genomics and Genetics (ACMG) guidelines using InterVar (19, 20). Germline variants classified as benign or uncertain significance by InterVar were discarded if their allele frequencies (AFs) are higher than 0.01 based on both 1000 Genomes Project(21) and gnomAD.(22) Somatic variants were further filtered by visual inspection of panel of normal data using Integrative Genomics Viewer (23). Both germline and somatic variants were annotated using Variant Effect Predictor (version 92)(24), and only the protein-altering variants were used for subsequent analyses (Table 3).

Copy-number alterations (CNAs) were identified using Control-FREEC. (25) For WES data, exonic regions were used as initial windows, and for WGS data, we used 5kb for both initial window and step size for CNA detection. Structural variations (SVs) were detected from WGS data using Meerkat (version 0.189) program (26). We set the standard deviation cutoff to call and cluster discordant repairs as 5 and the number of supporting split reads to call a SV event as 3.

Table 1(A). Summary of sequencing coverage

SampleID	Target region	Chr1	Chr2	Chr3	Chr4	Chr5	Chr6	Chr7	Chr8	Chr9	Chr10	Chr11	Chr12
09-110-N	whole exome	0.95	0.96	0.97	0.97	0.96	0.96	0.93	0.96	0.95	0.95	0.96	0.93
09-110-T	whole exome	0.96	0.96	0.98	0.97	0.97	0.96	0.94	0.96	0.96	0.96	0.96	0.94
09-323-N	whole exome	0.95	0.96	0.97	0.97	0.96	0.96	0.93	0.96	0.95	0.95	0.96	0.93
09-323-T	whole exome	0.96	0.96	0.98	0.97	0.97	0.97	0.94	0.96	0.96	0.96	0.97	0.94
09-679-N	whole exome	0.96	0.96	0.98	0.97	0.97	0.97	0.94	0.96	0.96	0.96	0.97	0.94
09-679-T	whole exome	0.95	0.95	0.97	0.96	0.96	0.95	0.93	0.95	0.95	0.95	0.96	0.93
11-1060-N	whole exome	0.96	0.96	0.98	0.97	0.97	0.96	0.94	0.96	0.95	0.95	0.96	0.94
11-1060-T	whole exome	0.95	0.96	0.97	0.97	0.96	0.96	0.94	0.95	0.96	0.95	0.96	0.93
11-849-N	whole exome	0.95	0.96	0.97	0.97	0.96	0.96	0.93	0.95	0.95	0.95	0.96	0.93
11-849-T	whole exome	0.94	0.94	0.96	0.96	0.95	0.95	0.92	0.94	0.93	0.94	0.95	0.92
3659-T	whole exome	0.95	0.95	0.97	0.97	0.96	0.95	0.93	0.95	0.95	0.95	0.95	0.93
3659-W	whole exome	0.96	0.96	0.98	0.97	0.97	0.96	0.94	0.96	0.95	0.95	0.96	0.94
FAM-100B	whole exome	0.93	0.93	0.95	0.93	0.94	0.94	0.91	0.93	0.93	0.93	0.94	0.91
FAM-100T	whole exome	0.93	0.94	0.94	0.94	0.94	0.94	0.90	0.94	0.92	0.92	0.93	0.90
TAR-06B	whole exome	0.88	0.90	0.88	0.87	0.87	0.89	0.85	0.84	0.86	0.88	0.84	0.86
TAR-06T	whole exome	0.88	0.90	0.89	0.87	0.88	0.89	0.85	0.82	0.86	0.88	0.83	0.87
09-110-N	whole genome	0.77	0.85	0.87	0.89	0.87	0.87	0.84	0.85	0.72	0.82	0.82	0.84
09-110-T	whole genome	0.84	0.93	0.94	0.95	0.94	0.94	0.94	0.92	0.78	0.90	0.90	0.91
09-323-N	whole genome	0.89	0.97	0.97	0.97	0.97	0.97	0.96	0.96	0.83	0.95	0.95	0.96
09-323-T	whole genome	0.90	0.98	0.98	0.98	0.98	0.98	0.97	0.97	0.85	0.97	0.97	0.97

09-679-N	whole genome	0.89	0.97	0.98	0.97	0.97	0.97	0.96	0.96	0.83	0.96	0.96	0.96
09-679-T	whole genome	0.90	0.97	0.98	0.98	0.98	0.97	0.97	0.97	0.84	0.96	0.96	0.97
11-1060-N	whole genome	0.90	0.97	0.98	0.98	0.98	0.97	0.97	0.97	0.84	0.96	0.97	0.97
11-1060-T	whole genome	0.89	0.97	0.98	0.97	0.98	0.97	0.97	0.97	0.84	0.96	0.96	0.97
11-849-N	whole genome	0.90	0.97	0.98	0.98	0.98	0.97	0.97	0.97	0.84	0.96	0.96	0.97
11-849-T	whole genome	0.90	0.97	0.98	0.98	0.98	0.97	0.97	0.97	0.84	0.96	0.97	0.97
3659-T	whole genome	0.89	0.97	0.98	0.98	0.98	0.97	0.96	0.97	0.84	0.96	0.96	0.97
3659-N	whole genome	0.88	0.96	0.97	0.97	0.97	0.97	0.95	0.96	0.82	0.95	0.95	0.96

SampleID	Chr13	Chr14	Chr15	Chr16	Chr17	Chr18	Chr19	Chr20	Chr21	Chr22	Average coverage
09-110-N	0.97	0.93	0.92	0.92	0.95	0.96	0.95	0.97	0.96	0.93	0.95
09-110-T	0.97	0.93	0.92	0.93	0.95	0.97	0.95	0.97	0.96	0.93	0.95
09-323-N	0.97	0.93	0.92	0.92	0.95	0.96	0.95	0.97	0.96	0.93	0.95
09-323-T	0.98	0.93	0.92	0.93	0.96	0.97	0.96	0.98	0.97	0.95	0.96
09-679-N	0.97	0.93	0.92	0.93	0.96	0.97	0.96	0.98	0.97	0.95	0.96
09-679-T	0.96	0.92	0.91	0.92	0.95	0.95	0.95	0.97	0.96	0.93	0.95
11-1060-N	0.97	0.93	0.92	0.92	0.95	0.96	0.95	0.97	0.96	0.94	0.95
11-1060-T	0.97	0.93	0.92	0.92	0.95	0.96	0.95	0.97	0.96	0.93	0.95
11-849-N	0.97	0.92	0.91	0.92	0.95	0.96	0.95	0.97	0.96	0.93	0.95
11-849-T	0.96	0.91	0.90	0.90	0.94	0.95	0.93	0.95	0.94	0.91	0.94
3659-T	0.97	0.92	0.91	0.92	0.94	0.96	0.95	0.96	0.96	0.93	0.95
3659-W	0.97	0.93	0.92	0.92	0.95	0.96	0.96	0.97	0.96	0.94	0.95
FAM-100B	0.94	0.90	0.89	0.90	0.93	0.93	0.93	0.95	0.94	0.92	0.93
FAM-100T	0.94	0.90	0.88	0.90	0.94	0.93	0.94	0.94	0.93	0.90	0.92
TAR-06B	0.88	0.84	0.86	0.80	0.88	0.86	0.78	0.84	0.85	0.81	0.86

TAR-06T	0.88	0.85	0.86	0.80	0.85	0.87	0.78	0.84	0.85	0.81	0.86
09-110-N	0.74	0.71	0.67	0.70	0.74	0.84	0.68	0.76	0.62	0.48	0.77
09-110-T	0.80	0.77	0.74	0.81	0.82	0.91	0.73	0.85	0.63	0.52	0.84
09-323-N	0.82	0.81	0.78	0.85	0.93	0.95	0.88	0.92	0.71	0.65	0.89
09-323-T	0.83	0.82	0.79	0.87	0.95	0.95	0.94	0.94	0.73	0.68	0.91
09-679-N	0.82	0.81	0.79	0.85	0.93	0.95	0.90	0.93	0.72	0.65	0.90
09-679-T	0.83	0.82	0.79	0.86	0.94	0.95	0.92	0.93	0.72	0.66	0.90
11-1060-N	0.83	0.82	0.79	0.86	0.95	0.95	0.92	0.94	0.72	0.67	0.91
11-1060-T	0.83	0.81	0.79	0.86	0.94	0.95	0.90	0.93	0.72	0.66	0.90
11-849-N	0.83	0.82	0.79	0.86	0.94	0.95	0.92	0.93	0.72	0.67	0.90
11-849-T	0.83	0.82	0.79	0.87	0.95	0.95	0.92	0.94	0.72	0.67	0.91
3659-T	0.83	0.81	0.79	0.86	0.94	0.95	0.90	0.93	0.72	0.66	0.90
3659-N	0.82	0.80	0.78	0.83	0.91	0.94	0.86	0.91	0.71	0.63	0.89

Table 1(B). Summary of sequencing depth

SampleID	Target region	Chr1	Chr2	Chr3	Chr4	Chr5	Chr6	Chr7	Chr8	Chr9	Chr10	Chr11	Chr12
09-110-N	whole exome	108.55	114.03	113.10	118.47	114.96	116.54	106.92	110.38	104.53	110.05	110.11	106.04
09-110-T	whole exome	124.37	132.58	131.02	138.64	133.96	135.20	146.99	127.53	120.23	126.47	126.48	120.96
09-323-N	whole exome	149.99	158.12	157.05	164.83	159.67	161.49	146.00	151.92	144.48	151.83	152.08	147.60
09-323-T	whole exome	176.18	177.41	179.01	179.85	194.16	184.37	169.04	175.26	171.61	175.15	182.17	169.83
09-679-N	whole exome	180.91	188.62	188.20	194.81	190.49	192.90	176.75	182.10	175.41	184.15	184.86	176.94
09-679-T	whole exome	117.23	118.87	133.19	121.56	120.73	122.65	126.22	117.14	114.29	117.11	120.65	113.80
11-1060-N	whole exome	144.18	150.04	149.13	155.25	151.79	153.78	140.89	145.93	139.64	146.81	147.02	141.31
11-1060-T	whole exome	133.78	141.20	139.05	143.76	141.09	167.84	178.14	135.05	145.70	134.35	137.52	130.08
11-849-N	whole exome	141.39	147.78	147.14	153.23	148.95	151.56	138.64	143.47	137.27	144.67	144.37	138.49
11-849-T	whole exome	112.69	120.10	132.94	125.35	129.42	122.06	124.34	115.52	109.71	114.92	115.71	123.57
3659-T	whole exome	139.69	137.05	135.78	142.97	137.92	140.19	126.71	132.56	125.65	131.63	132.55	127.33
3659-W	whole exome	174.21	181.15	180.63	187.53	182.65	186.28	168.80	175.23	168.21	175.64	177.20	170.79
FAM-100B	whole exome	82.90	81.09	83.04	79.38	83.03	85.87	78.97	79.06	81.28	82.79	86.56	78.76
FAM-100T	whole exome	114.79	126.73	113.49	112.26	114.32	131.69	102.08	125.83	109.16	113.19	115.81	109.10
TAR-06B	whole exome	66.24	84.36	66.84	67.33	67.78	69.72	66.42	79.38	64.38	66.13	62.65	65.35
TAR-06T	whole exome	80.13	93.05	83.95	93.40	86.70	86.52	82.51	78.59	77.12	82.57	74.14	82.01
09-110-N	whole genome	21.54	22.31	22.40	22.35	22.73	22.63	21.81	21.76	19.09	21.00	22.57	23.15
09-110-T	whole genome	24.26	26.04	26.35	27.19	26.73	26.87	30.43	25.74	21.93	24.38	25.96	26.18
09-323-N	whole genome	33.32	37.69	38.34	39.93	38.74	38.23	36.54	38.11	30.84	35.14	35.70	36.38
09-323-T	whole genome	46.99	51.57	51.95	52.81	55.76	51.88	50.45	52.05	43.08	49.34	49.88	50.38

09-679-N	whole genome	31.63	35.58	36.06	37.36	36.24	35.88	34.66	35.74	29.29	33.67	33.91	34.36
09-679-T	whole genome	44.67	50.60	56.23	53.50	51.73	51.24	53.71	51.00	41.75	47.26	47.91	48.95
11-1060-N	whole genome	37.36	41.59	41.93	43.12	42.28	41.86	40.85	42.01	34.38	39.83	39.90	40.46
11-1060-T	whole genome	43.61	50.34	50.54	52.84	51.05	56.40	66.26	50.22	42.12	45.94	46.88	47.74
11-849-N	whole genome	38.09	43.11	43.78	45.42	44.03	43.55	42.10	43.47	35.23	40.56	41.04	41.62
11-849-T	whole genome	45.64	52.12	65.10	55.54	59.31	52.57	62.11	52.61	42.41	48.32	49.34	61.18
3659-T	whole genome	39.55	42.44	43.17	45.07	43.42	42.95	41.14	42.91	35.19	39.45	40.32	40.88
3659-N	whole genome	32.57	36.87	37.57	39.32	37.83	37.44	35.87	37.36	30.57	34.30	34.92	35.62

SampleID	Chr13	Chr14	Chr15	Chr16	Chr17	Chr18	Chr19	Chr20	Chr21	Chr22	Average depth
09-110-N	121.91	106.18	101.57	97.80	102.17	109.56	96.88	102.99	107.44	91.14	107.79
09-110-T	142.88	120.57	114.80	129.31	113.32	128.67	103.24	116.92	99.47	89.42	123.77
09-323-N	169.16	146.00	140.48	132.77	139.32	154.27	129.74	141.00	147.49	123.58	148.58
09-323-T	185.24	169.81	162.17	194.95	175.82	171.42	172.80	173.67	174.30	160.43	176.12
09-679-N	200.18	176.13	169.25	164.21	171.55	181.76	161.46	173.38	177.53	154.24	179.36
09-679-T	123.94	113.40	108.18	124.25	127.98	115.89	114.78	127.73	129.08	105.59	119.74
11-1060-N	159.05	140.57	135.00	131.78	137.23	145.17	130.44	138.07	142.58	123.23	143.13
11-1060-T	147.00	129.94	125.55	160.23	126.65	136.05	120.04	128.75	129.62	114.88	138.47
11-849-N	157.19	138.17	131.73	130.05	135.18	142.97	125.84	135.54	140.81	120.26	140.67
11-849-T	128.37	110.04	104.42	110.44	115.69	116.61	94.40	106.71	111.64	92.82	115.34
3659-T	146.92	126.15	121.10	152.82	121.58	134.45	112.78	123.07	128.31	108.18	131.15
3659-W	192.43	169.31	162.53	158.07	165.27	176.76	157.55	166.18	170.71	148.03	172.51
FAM-100B	82.15	80.00	77.13	81.14	83.84	80.19	82.09	84.46	83.67	77.13	81.57
FAM-100T	116.35	107.96	89.28	113.96	162.50	108.69	118.30	115.68	116.63	95.51	115.15
TAR-06B	62.68	63.48	67.23	55.77	79.83	59.71	53.21	57.99	61.38	53.21	65.50

TAR-06T	86.86	78.79	82.22	61.54	68.89	85.83	61.81	63.87	73.15	56.43	78.19
09-110-N	18.44	19.36	18.42	21.00	23.10	20.23	22.68	20.11	17.46	14.69	20.86
09-110-T	22.47	21.72	20.44	27.30	23.97	24.69	21.73	22.40	16.28	13.63	23.94
09-323-N	33.28	30.98	28.54	30.89	29.96	37.03	25.77	31.66	28.79	19.32	33.42
09-323-T	44.19	42.92	40.63	50.82	46.02	50.25	42.47	46.66	39.94	31.03	47.32
09-679-N	31.19	29.19	27.27	29.32	28.88	34.55	25.15	30.45	26.95	18.87	31.65
09-679-T	44.47	41.62	38.62	44.29	44.09	49.66	35.37	46.01	41.46	25.70	45.90
11-1060-N	36.00	34.32	33.36	35.51	35.46	40.54	31.42	36.56	31.97	23.46	37.46
11-1060-T	43.98	40.62	38.64	51.34	38.79	48.97	32.63	41.24	37.14	24.57	45.54
11-849-N	37.89	35.47	32.85	35.40	35.02	41.99	29.90	36.69	32.90	22.92	38.32
11-849-T	46.25	42.70	39.07	49.44	49.31	51.21	34.21	43.35	39.58	26.40	48.54
3659-T	37.56	34.66	32.18	45.34	33.99	41.89	28.93	35.74	32.58	21.78	38.23
3659-N	32.71	30.16	27.97	30.40	29.30	36.29	25.07	30.76	28.34	18.50	32.72

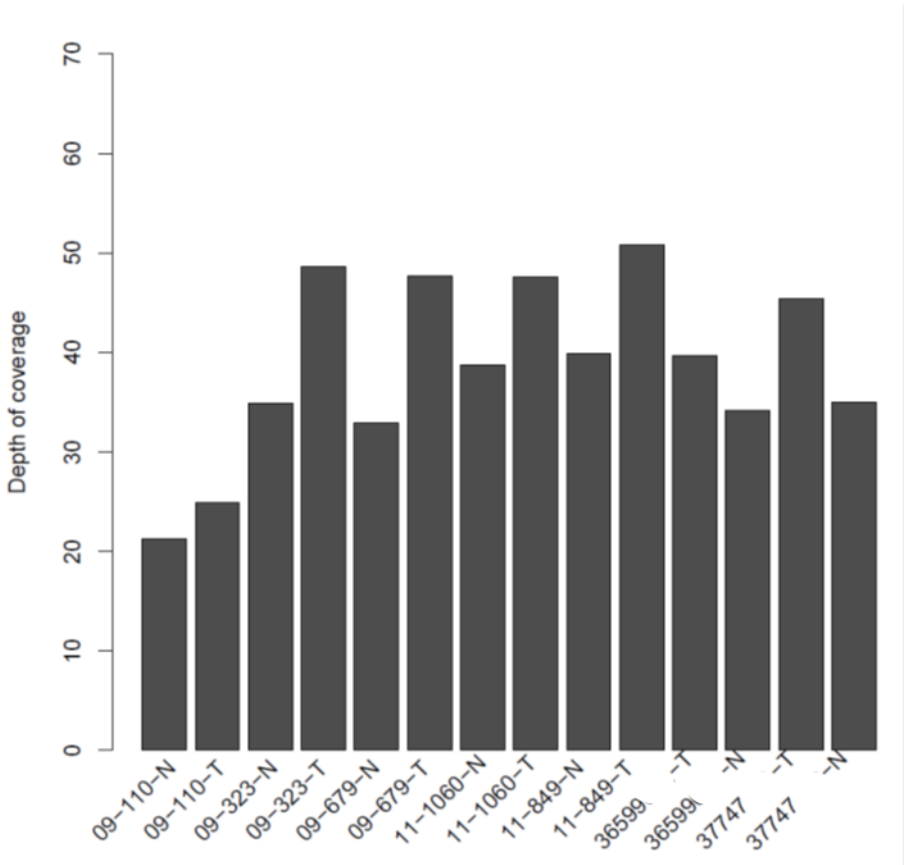


Figure 1. Average Depth of coverage of whole genome sequencing

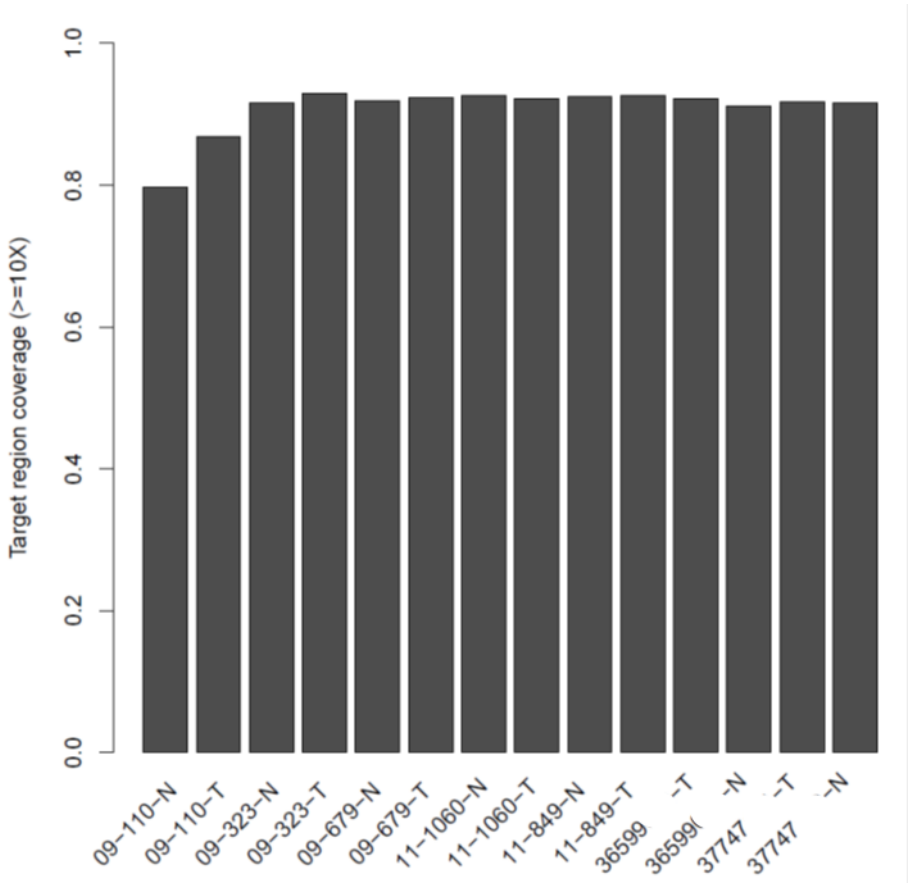


Figure 2. Target region coverage (≥10x) bar plot for whole genome sequencing

Ethics

We obtained informed consent from all subjects, and this study was reviewed and approved by the Institutional Review Board of Seoul National University Hospital (IRB approval number: 1204-026-403). This was conducted in accordance with the Principles of the Declaration of Helsinki.

Results

Clinical characteristics of patients with PRCC type 2

We obtained a total of seven PRCC2 tissues and paired normal samples. The clinical characteristics of the patients are described in Table 2. Of seven patients, only one was female. Median age at cancer diagnosis was 51 (range 25–82). Four patients underwent curative resection of PRCC2 and these patients were alive without metastasis, however, three patients with metastatic disease received systemic chemotherapy and ultimately died due to disease progression.

The systemic treatments administered to patients with metastatic disease are listed in Table 2B. All three patients received temsirolimus as first-line systemic treatment. After disease progression, two patients received axitinib and one patient received high-dose interleukin-2 as second-line treatment.

Pathology review was also performed (Figure 3) and one case was missed. Of six cases, five cases of PRCC2 were compatible to be diagnosed with PRCC type 2 and one case was re-diagnosed with HLRCC associated RCC.

Table2. Clinical information of papillary renal cell carcinoma type 2

(A). Clinical and pathological baseline characteristics

	Age (YO)[1]	Sex	Smoking (Pack year)	Stage	Grade	FU (Mo) [2]	Status	Tumor	Normal	Sampletype
1	30	M	13	3	4	95.20	NED[3]	Kidney[6]	Kidney	Freshfrozen
2	74	M	60	1	3	46.83	NED	Kidney[6]	Kidney	Freshfrozen
3	82	M	Never	4	3	69.40	Dead	Kidney[6]	Kidney	Freshfrozen
4	63	M	Never	1	3	81.17	NED	Kidney[6]	Kidney	Freshfrozen
5	51	M	20	1	3	108.60	NED	Kidney[6]	PB[4]	Freshfrozen
6	27	M	Never	4	NA	14.50	Dead.	Bone[7]	PB	FFPE[5]
7	26	F	Never	4	3	35.83	Dead	Kidney[7]	PB	FFPE

[1]Year-old; [2]Months; [3]No evidence of disease; [4]Peripheral blood; [5]Formalin fixed paraffin embedded; [6]Surgical specimen; [7]Percutaneous needle biopsy specimen

(B). Medical treatment of stage IV PRCC2 patients.

.	Metastasis Sites	Treatment	No.of cycle	Time to Progression (weeks)	Best Response	Treatment off
3	Lung	Temsirolimus	Week 12	23	SD[1]	Adverse event
	Adrenal gland	Axitinib	22	87	PR[2]	Patient wish
6	Bone, liver,	Temsirolimus	Week 4	4	PD[3]	PD[3]
	Lymph node	Axitinib	1	4	PD[3]	PD[3]
		Gemcitabine plus cisplatin	1	4	PD[3]	PD[3]

		Pembrolizumab	2	2	PD[3]	PD[3]
		Bevacizumab + erlotinib‡	13	40	SD[1]	PD[3]
		Nivolumab+ipilimumab	1	2	PD[3]	PD[3]
7	Bone	RTx1*				PD[3]
	Liver	Temsirolimus	Week 26	26	SD[1]	PD[3]
	Adrenal gland	High dose interleukin-2	6	19	SD[1]	PD[3]
	Peritoneum	RTx2[†]				PD[3]
		Pazopanib‡	14	52	PR[2]	PD[3]

*Tomotherapy at bone metastasis; [†]Tomotherapy at bone, adrenal gland, abdomen wall, pelvis metastasis; ‡Precision treatment using NGS data; [1]Stable disease; [2]Partial response; [3]Progressive disease

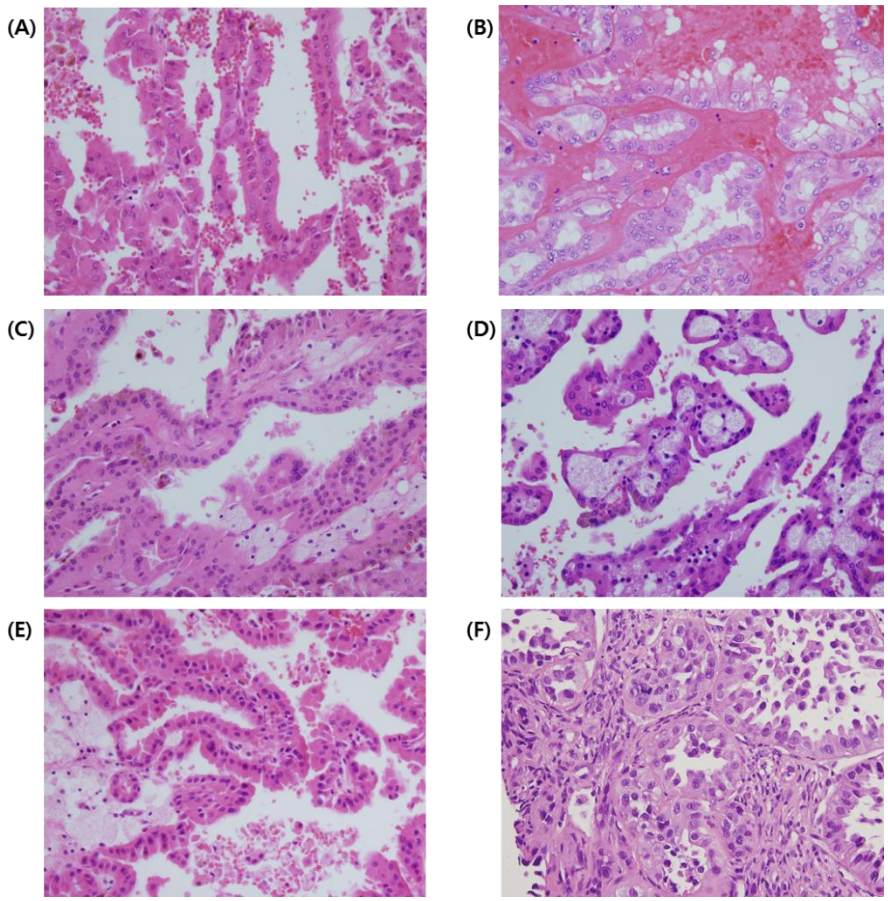


Figure 3. H&E stain of six papillary renal cell carcinoma type 2 (PRCC2) of (A) M/30, (B) M/72, (C)M/82, (D)M/63, (E)M/51 and (F) M/27 cases

H&E slides suggest (A)-(E) are compatible to be diagnosed with PRCC2 and (F) case is HLRCC associated RCC

Germline and somatic SNVs/indels

We described the number of somatic mutation according to functional and non-functional mutation in Figure 4,5 and 6. In addition, region of genetic alterations were analyzed (Figure 7). From whole-genome and exome sequencing analysis, we determined germline and somatic SNVs/indels (Figure 8) (Table 3). In terms of germline mutations, a wide range of known cancer genes involved in various kinds of biological processes such as positive regulation of biosynthetic process, phosphate containing compound metabolic process, tissue development, and others were seemed to be affected by potentially functional rare germline variants reflecting the heterogeneous nature of PRCC2.

Among a few recurrently mutated genes by germline variants, *FH* germline mutations were detected in two patients (Figure 8). For the patients with metastatic disease, one with familial leiomyoma had a germline missense mutation of *FH* (p.Lys230Glu) (Figure 9A), and the other patient without family history of HLRCC harbored a germline splicing site mutation (c.1108+1G>A) in *FH* (Figure 9B).

Other germline mutations were also found in PRCC2 (Figure 7) (Table 3). Germline*MKL1*, *NACA*, *PRDM16*, *TET2*, *RGPD3*, *CSMD3* and *KMT2C* alterations were found in more than one PRCC2 sample. Genetic alterations were present in different loci of

coding region. In addition, *BRCA1, BRCA2* and *PMS2* germline mutations were also detected. In terms of functional alteration according to base change, *BRCA1* alteration (p.Lys181Gln), *BRCA2* (p.Gly2508Ser) and *PMS2* (p.Val196Phe) resulted in amino acid changes be deleterious by SIFT prediction.(27) In addition, 16 genes were affected by pathogenic or likely pathogenic germline mutations based on the ACMG criteria in at least one patient. Among them *ALDH2*, *BCR*, *FH* and *NBEA* genes were known cancer driver genes according to COSMIC Cancer Gene Census database(28) identified. (Table 3)

A significant number of somatic mutations were detected from tissue development-related genes such as *SETD2*, *COL2A1*, *FLNA*, *NF2*, *NOTCH2*, and *RAD51B*. Especially, *SETD2* was altered also by germline mutation in other samples (Figure 8). Interestingly, a somatic *FH* frameshift deletion (p.Leu132Ter) was detected from the patient with metastatic disease who already harbored the germline splicing site mutation (c.1108+1G>A) (Figure 9B).

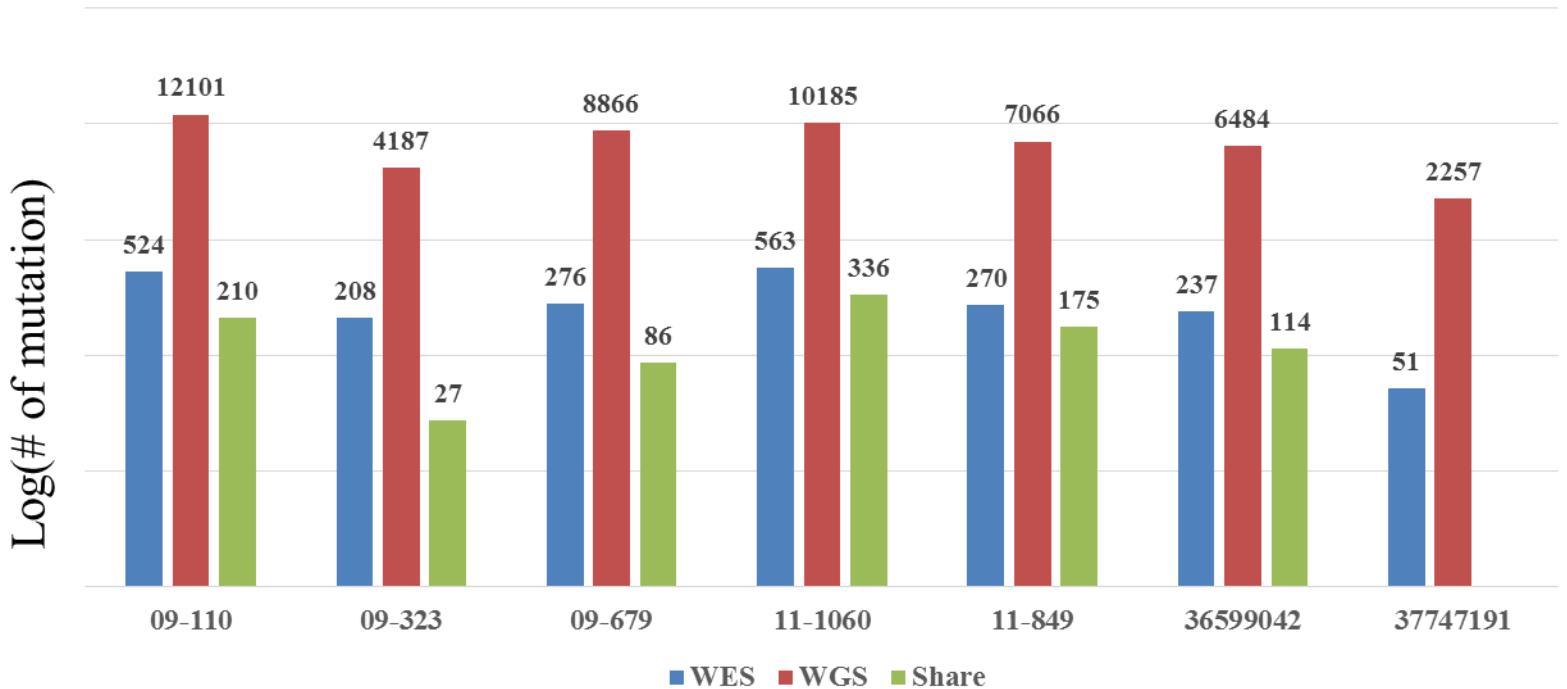


Figure 4. Number of somatic mutation

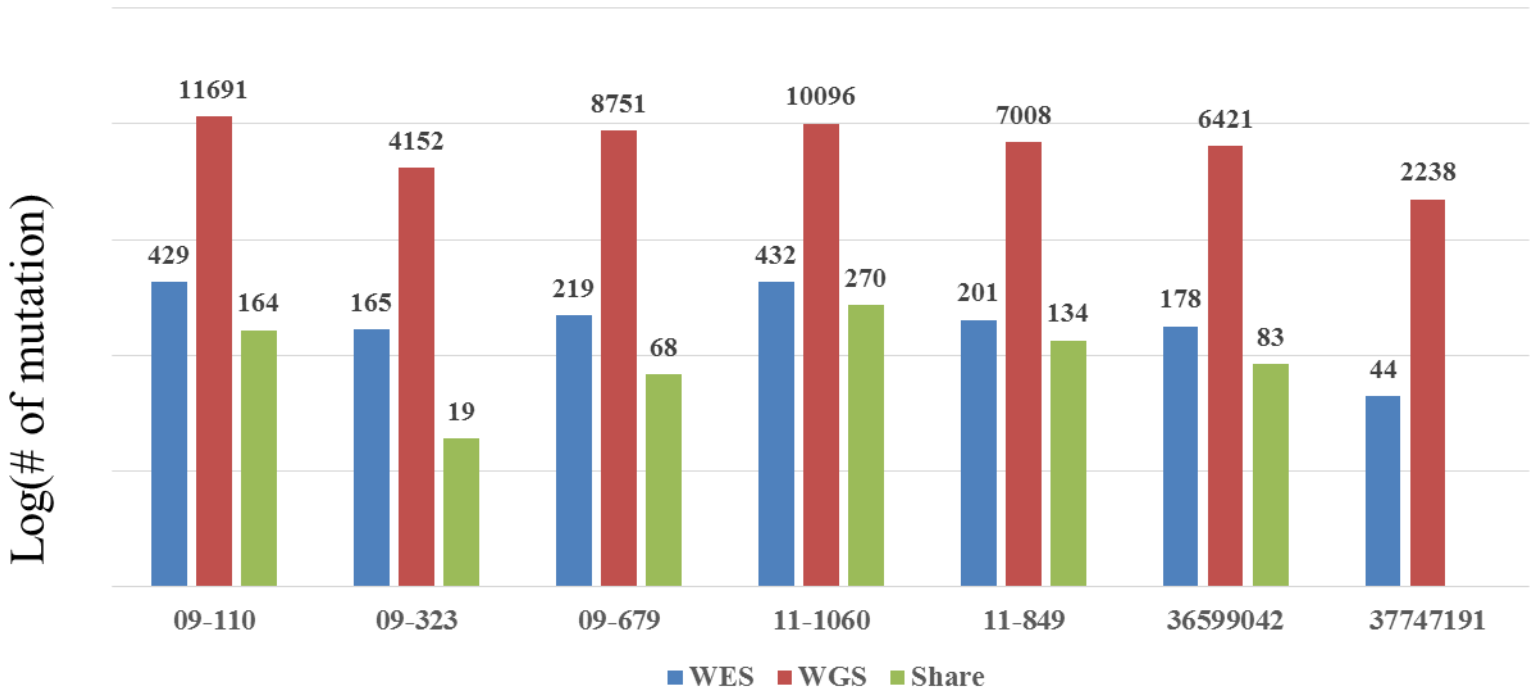


Figure5. Number of non-functional somatic mutation

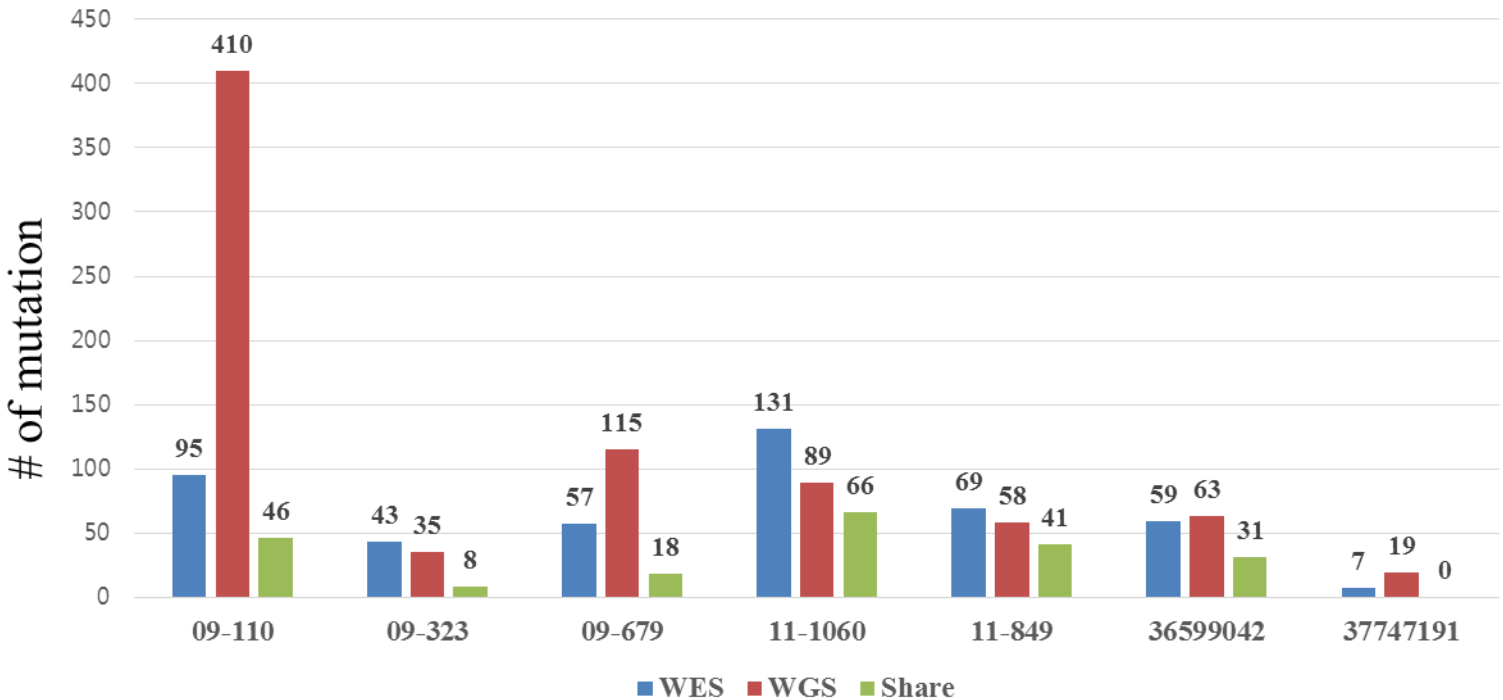


Figure 6. Number of functional somatic mutation

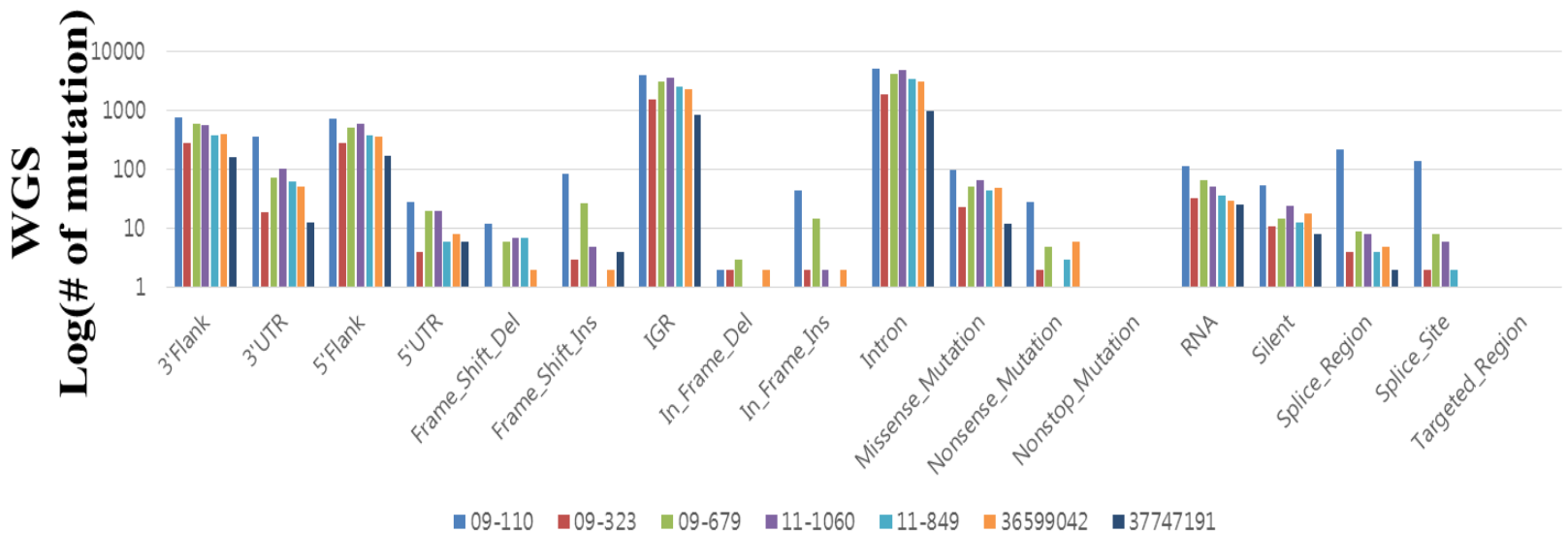


Figure 7. Number of somatic mutation according to coding regions

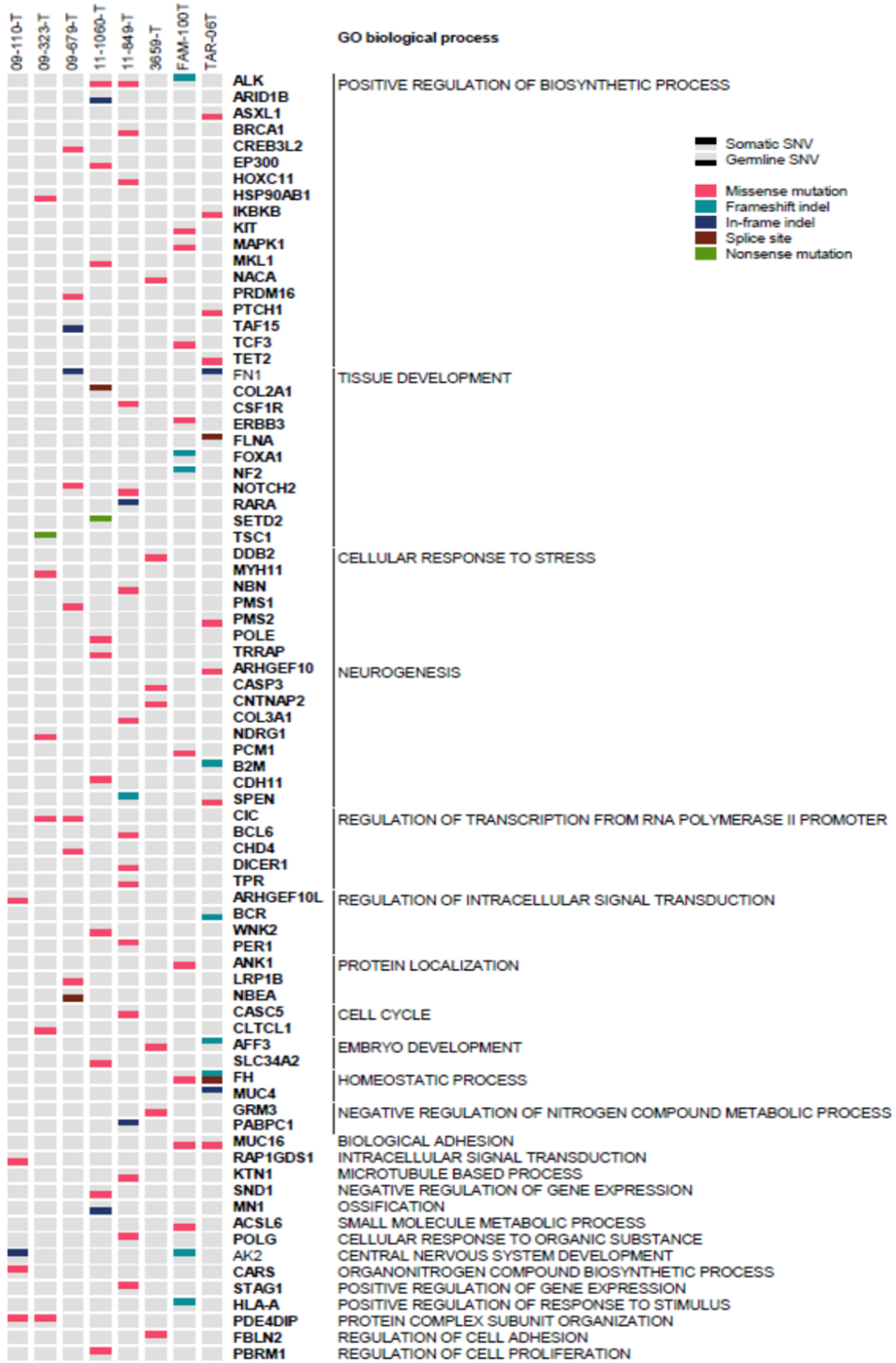


Figure 8. Germline and somatic mutations in papillary renal cell carcinoma type 2 (PRCC2) (Known cancer-related gene based on the Cancer Gene Consensus of COSMIC database are shown in bold letters).

Table 3. The final set of filtered germline and somatic mutations

Sample	Gene	Variant class	Variant type	Cancer gene concensus
09-110-T	AK2	In_Frame_Ins	Somatic	F
09-110-T	ARHGEF10L	Missense_Mutation	Germline	T
09-110-T	CARS	Missense_Mutation	Somatic	T
09-110-T	PDE4DIP	Missense_Mutation	Somatic	T
09-110-T	RAP1GDS1	Missense_Mutation	Germline	T
09-323-T	CIC	Missense_Mutation	Germline	T
09-323-T	CLTCL1	Missense_Mutation	Germline	T
09-323-T	CLTCL1	Missense_Mutation	Germline	T
09-323-T	HSP90AB1	Missense_Mutation	Germline	T
09-323-T	MYH11	Missense_Mutation	Germline	T
09-323-T	NDRG1	Missense_Mutation	Germline	T
09-323-T	PDE4DIP	Missense_Mutation	Somatic	T
09-323-T	TSC1	Nonsense_Mutation	Somatic	T
09-679-T	CHD4	Missense_Mutation	Germline	T
09-679-T	CIC	Missense_Mutation	Germline	T
09-679-T	CREB3L2	Missense_Mutation	Germline	T
09-679-T	LRP1B	Missense_Mutation	Germline	T
09-679-T	NBEA	Splice_Site	Germline	T
09-679-T	NOTCH2	Missense_Mutation	Somatic	T
09-679-T	PMS1	Missense_Mutation	Germline	T
09-679-T	PRDM16	Missense_Mutation	Germline	T
09-679-T	TAF15	Missense_Mutation	Germline	T
09-679-T	TAF15	In_Frame_Ins	Germline	T
11-1060-T	ALK	Missense_Mutation	Germline	T
11-1060-T	ARID1B	In_Frame_Ins	Germline	T
11-1060-T	CDH11	Missense_Mutation	Somatic	T
11-1060-T	COL2A1	Splice_Site	Somatic	T
11-1060-T	EP300	Missense_Mutation	Germline	T
11-1060-T	MKL1	Missense_Mutation	Germline	T
11-1060-T	MN1	In_Frame_Ins	Germline	T
11-1060-T	PBRM1	Missense_Mutation	Somatic	T

11-1060-T	POLE	Missense_Mutation	Germline	T
11-1060-T	SETD2	Nonsense_Mutation	Somatic	T
11-1060-T	SLC34A2	Missense_Mutation	Germline	T
11-1060-T	SND1	Missense_Mutation	Germline	T
11-1060-T	TRRAP	Missense_Mutation	Germline	T
11-1060-T	WNK2	Missense_Mutation	Germline	T
11-849-T	ALK	Missense_Mutation	Germline	T
11-849-T	BCL6	Missense_Mutation	Germline	T
11-849-T	BRCA1	Missense_Mutation	Germline	T
11-849-T	CASC5	Missense_Mutation	Germline	T
11-849-T	COL3A1	Missense_Mutation	Germline	T
11-849-T	CSF1R	Missense_Mutation	Somatic	T
11-849-T	DICER1	Missense_Mutation	Germline	T
11-849-T	HOXC11	Missense_Mutation	Germline	T
11-849-T	KTN1	Missense_Mutation	Germline	T
11-849-T	NBN	Missense_Mutation	Germline	T
11-849-T	NOTCH2	Missense_Mutation	Germline	T
11-849-T	PABPC1	In_Frame_Ins	Somatic	T
11-849-T	PER1	Missense_Mutation	Somatic	T
11-849-T	POLG	Missense_Mutation	Somatic	T
11-849-T	RARA	In_Frame_Del	Somatic	T
11-849-T	SPEN	Frame_Shift_Del	Somatic	T
11-849-T	STAG1	Missense_Mutation	Somatic	T
11-849-T	TPR	Missense_Mutation	Germline	T
3659-T	AFF3	Missense_Mutation	Germline	T
3659-T	CASP3	Missense_Mutation	Germline	T
3659-T	CNTNAP2	Missense_Mutation	Germline	T
3659-T	DDB2	Missense_Mutation	Germline	T
3659-T	FBLN2	Missense_Mutation	Somatic	T
3659-T	GRM3	Missense_Mutation	Germline	T
3659-T	NACA	Missense_Mutation	Germline	T
FAM-100T	ACSL6	Missense_Mutation	Germline	T
FAM-100T	AK2	Frame_Shift_Ins	Somatic	F
FAM-100T	ALK	Frame_Shift_Ins	Somatic	T
FAM-100T	ANK1	Missense_Mutation	Germline	T

FAM-100T	ERBB3	Missense_Mutation	Somatic	T
FAM-100T	FH	Missense_Mutation	Germline	T
FAM-100T	FOXA1	Frame_Shift_Ins	Somatic	T
FAM-100T	HLA-A	Frame_Shift_Ins	Somatic	T
FAM-100T	KIT	Missense_Mutation	Germline	T
FAM-100T	MAPK1	Missense_Mutation	Germline	T
FAM-100T	MUC16	Missense_Mutation	Germline	T
FAM-100T	NF2	Frame_Shift_Ins	Somatic	T
FAM-100T	PCM1	Missense_Mutation	Germline	T
FAM-100T	TCF3	Missense_Mutation	Germline	T
TAR-06T	AFF3	Frame_Shift_Del	Somatic	T
TAR-06T	ARHGEF10	Missense_Mutation	Germline	T
TAR-06T	ASXL1	Missense_Mutation	Germline	T
TAR-06T	B2M	Frame_Shift_Ins	Somatic	T
TAR-06T	BCR	Frame_Shift_Ins	Germline	T
TAR-06T	FH	Frame_Shift_Del	Somatic	T
TAR-06T	FH	Splice_Site	Germline	T
TAR-06T	FLNA	Splice_Site	Somatic	T
TAR-06T	IKBKB	Missense_Mutation	Germline	T
TAR-06T	MUC16	Missense_Mutation	Germline	T
TAR-06T	PMS2	Missense_Mutation	Germline	T
TAR-06T	PTCH1	Missense_Mutation	Germline	T
TAR-06T	SPEN	Missense_Mutation	Germline	T
TAR-06T	TET2	Missense_Mutation	Germline	T

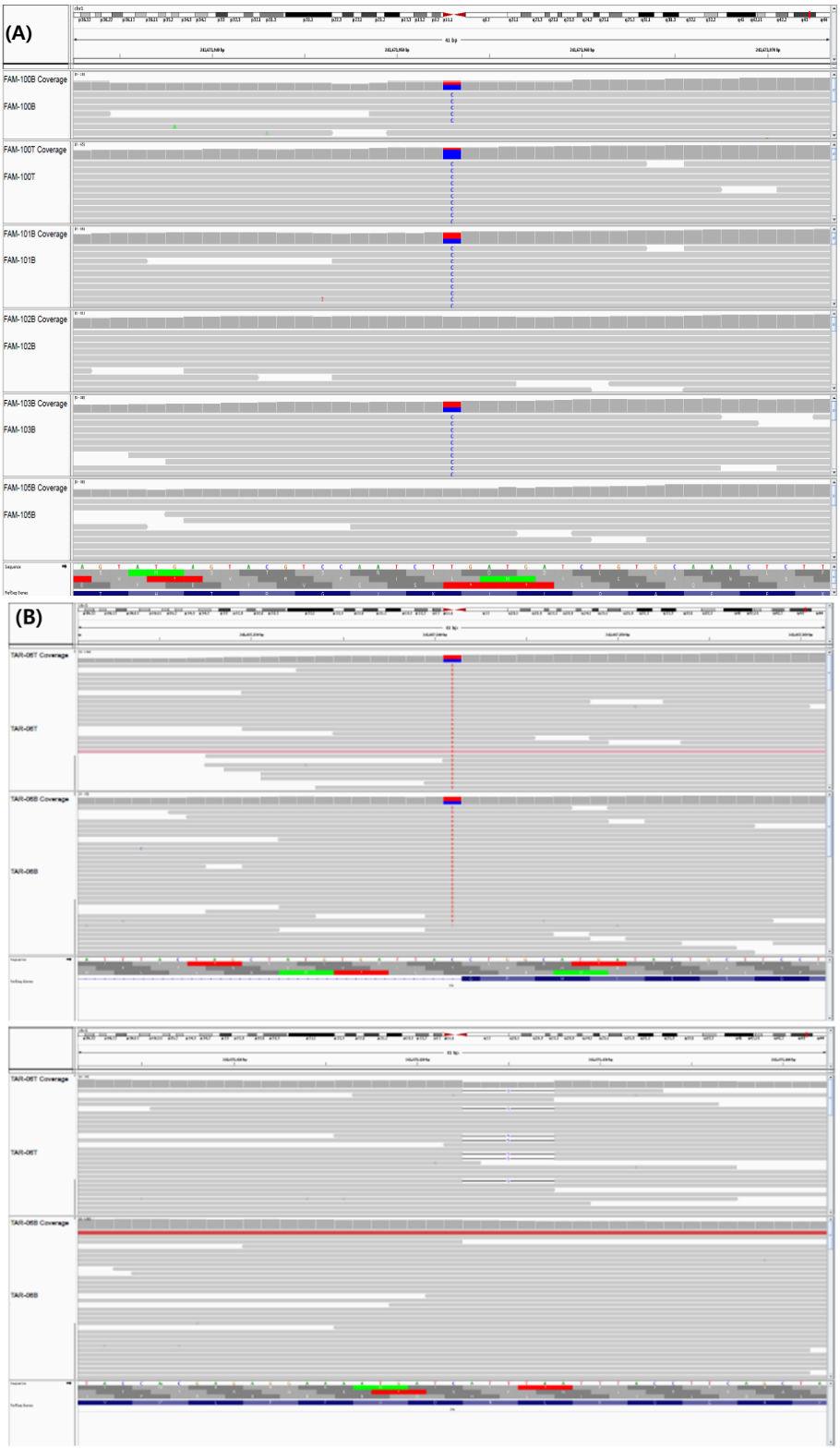

(A)
FAM-100B Coverage
FAM-100B
FAM-100T Coverage
FAM-100T
FAM-101B Coverage
FAM-101B
FAM-102B Coverage
FAM-102B
FAM-103B Coverage
FAM-103B
FAM-105B Coverage
FAM-105B
(B)
TAR-08T Coverage
TAR-08T
TAR-08B Coverage
TAR-08B
TAR-08T Coverage
TAR-08T
TAR-08B Coverage
TAR-08B

Figure 9. IGV snapshot of *FH* alterations in (A) family with HLRCC (B) patient with both germline and somatic *FH* mutation

Copy number alterations and structure variations

CNAs were analyzed using both whole-exome and whole-genome sequencing data. Recurrent copy number gains of chromosome 7, 16, and 17 were observed in our data (Figure 10), which is well concordant with that reported by The Cancer Genome Atlas (7). Other than chromosomal copy number alterations, recurrent focal amplifications of potential oncogenes such as *MYC4, IRF4* and *NUP98* were identified. Frequent copy number losses of *TNFRSF14, FGFR3, STK11*, and*SEPT5* that are known to have tumor suppressor properties were also found. For SV analysis, we used whole-genome sequencing data and identified average 34.3 SV events (sd: 29.7) per samples. We identified a number of gene fusions in PRCC2 samples but none affecting known cancer driver genes (Figure 11).

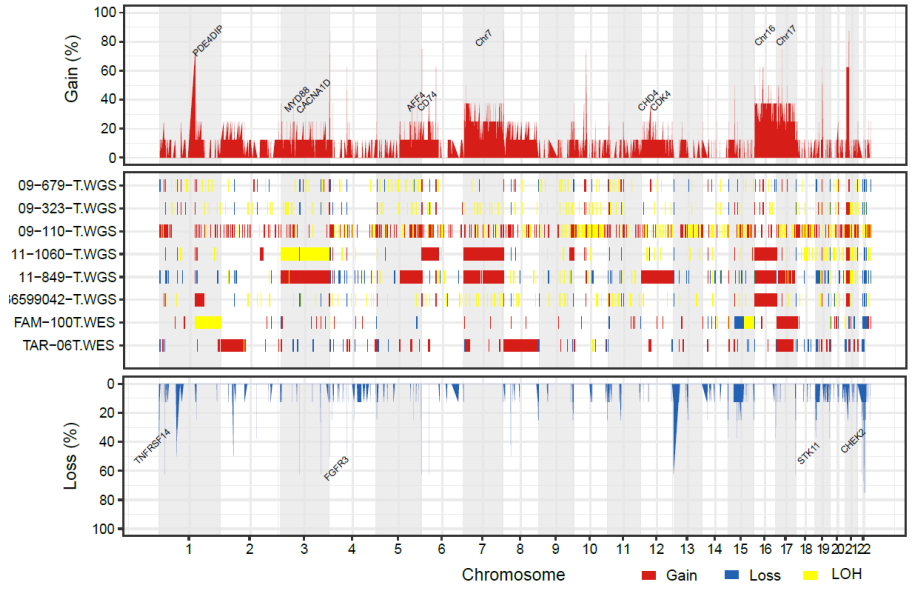


Figure 10. Copy number alterations detected from the eight PRCC2 sequencing data (WGS: genome sequencing, WES: exome sequencing)

Figure 11. Structural variation identified from whole-genome sequencing data

Impact of genetic alterations on prognosis of patients

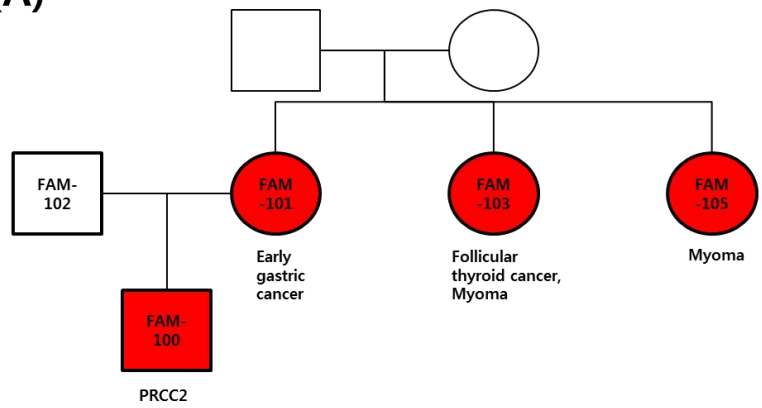
We evaluated the effect of genetic alterations on patient prognosis (Table 2). Regardless of genetic alterations, primary carcinoma that received curative surgery did not recur. Three patients with metastatic carcinomas were treated with systemic chemotherapy and eventually died due to disease progression. Two of the three patients with metastatic disease had genetic alteration of *FH*. The patient without genetic alteration of *FH* showed a durable response to temsirolimus (mTOR inhibitor) and axitinib (a tyrosine kinase inhibitor [TKI], which targets vascular endothelial growth factor-receptor 1-3 [VEGFR 1-3]).

One patient with familiar history of leomyoma had a germline missense mutation of *FH*. Among his family, his mother and her sisters have been diagnosed with myoma, thyroid cancer, and early gastric cancer (Figure 12A). Germline *FH* mutation testing of his family members revealed germline missense mutation of *FH* at the same locus in his maternal family members but absent in his father (Figure 9A). In clinical course, this patient did not respond to mTOR inhibitor, VEGFR TKI, cytotoxic chemotherapy, or the anti-PD1 antibody pembrolizumab (Table 2B). After we found the *FH* germline mutation, the patient was treated with a combination of bevacizumab (an anti-VEGF antibody) and erlotinib (an epithelial growth factor receptor [EGFR] TKI) and showed a durable response (Figure 12B).

A young patient with germline and somatic *FH* mutations was treated with pazopanib, a selective multi-targeted receptor TKI, after her genetic alteration was revealed (Table 2B). Pazopanib resulted in a decrease in the tumor over one year, but grade 3 lethargy developed and resulted in treatment discontinuation (Figure 13A).

Other patient with metastatic PRCC2 harboring *PBRM1* and *SETD2* mutations had relatively long survival duration. He responded axitinib treatment for a long duration until adverse events forbade him from receiving treatment (Table 2B) (Figure 13B).

(A)



(B)

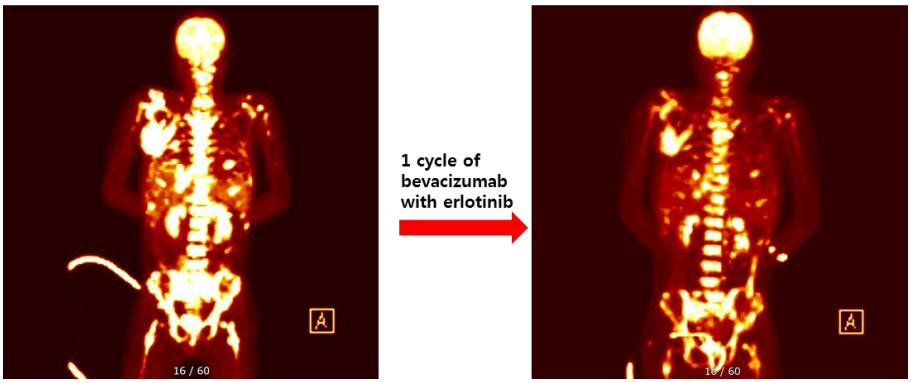


Figure 12. (A) Pedigree of family with hereditary leiomyoma renal cell carcinoma (B) Treatment response after 1cycle of bevacizumab with erlotinib treatment in patient with HLRCC (PRCC type 2)

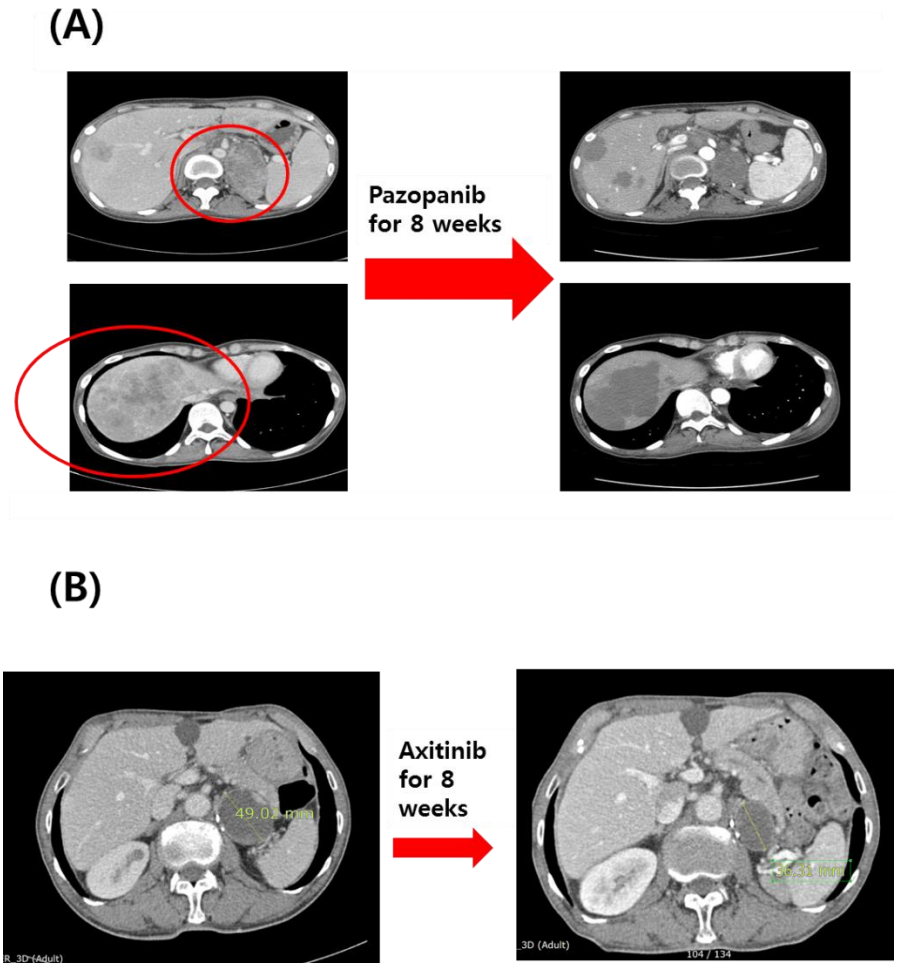


Figure 13. (A) Treatment response after pazopanib in PRCC2 with somatic *FH* mutation (B) Treatment response after axitinib in PRCC2 with *PBRM1* mutation

Discussion

In this study, we identified genetic alterations in PRCC2. Mutation in the gene encoding fumarate hydratase, either germline or somatic, was found in patients younger than 30 years and indicated poor prognosis. In terms of treatment, patients harboring *FH* mutation responded to anti-angiogenesis agents including bevacizumab and pazopanib.

Current treatment guideline of renal cell carcinoma is based on their histology (29). In terms of ccRCC, immune check point inhibitor combined with multi-tyrosine kinase inhibitor(TKI) is the front line of standard treatment. However, there is different treatment strategy for non-clear cell renal cell carcinoma. Preferred regimen for nccRCC is clinical trial or sunitinib according to National Comprehensive Cancer Network(NCCN) treatment guideline. Among nccRCC, only bevacizumab with elrotinib is the standard treatment regiemen for HLRCC associated RCC. Therefore, finding genetic alteration is important to treat nccRCC precisely.

PRCC is defined as non-clear cell renal cell carcinoma (nccRCC) with a papillary pattern based on pathologic finding (1). Type 2 PRCC is lined by large cells with abundant eosinophilic cytoplasm compared to the small cells with clear to basophilic cytoplasm present in type 1 PRCC. The best-known genetic alteration of type 1 PRCC is *MET*

mutation, whereas *FH* nutation is common in type 2, especially in familial cases (30). However, with the exception of familial cases of PRCC, genetic alterations that drive tumorigenesis of PRCC2 have not been revealed. Recent genetic analysis showed that PRCC2 could be classified into three subgroups according to molecular differences (7). One subgroup represented by *FH* mutation and *CDKN2A* silencing due to hypermethylation of the *CDKN2A* promoter had a relatively small number of PRCC2 (13.3%). This subgroup was characterized by relatively young patients and extremely short survival duration compared to other subtypes. In our study, two young patients with *FH* mutated PRCC2 had similar clinical characteristics to this subtype.

Fumarate hydratase (*FH*), a tricarboxylic acid cycle (TCA) enzyme, catalyzes the hydration of fumarate into malate. Deficiency of *FH* causes accumulation of fumarate and activation of hypoxia inducible factor (*HIF*) under normal oxygen levels (31). VEGF and glucose transporter-1(*GLUT-1*) are upregulated by an excess of intracellular fumarate through the HIF-dependent pathway. Therefore, inhibition of the VEGF pathway and glucose transport has been suggested as a therapeutic approach in *FH* mutant cancer (31, 32). In our study, we identified two patients with PRCC2 harboring *FH* mutation characterized by rapid progression. One patient with germline *FH* mutation did not respond to axitinib, a selective VEGFR inhibitor, but

did respond to bevacizumab and erlotinib combination therapy (33). Another patient was treated using pazopanib, a multi-targeted receptor TKI whose targets include VEGFR, and she only responded to this treatment. The mechanism of action of pazopanib does not include glucose metabolism, but hypoglycemia frequently occurs during pazopanib treatment (34). With regard to this adverse event, pazopanib might modify glucose metabolism in *FH* mutant PRCC2. Therefore, based on our clinical experience, a therapeutic strategy for *FH* mutant PRCC2 should consider targeting glucose metabolism in addition to inhibition of the VEGF pathway.

The Warburg effect(35), a metabolic shift to aerobic glycolysis in normoxia status, is one of the characteristics of *FH* mutant RCC (33). This ineffective metabolism in tumor cells resulting from the rapid proliferation of cancer cells might induce cachexia of patients (36). In our study, the patient treated with pazopanib suffered cancer-related cachexia even though her disease was well controlled. Consequentially, her general condition gradually deteriorated, and she could not undergo further treatment.

Pathogenic germline alteration of *C7*, *FH*, *MAK*, *NBEA*, *NDUFS1* and *TTC37* were also detected in this study. Mutations in *NDUFS1*, the largest subunit of mitochondrial complex I, are known to reduce the activity of complex I (37). We also identified ten likely pathogenic

germline mutations in *ALDH1A3, ALDH2, APOE, BCR, CCNL1*, *COL4A2, EYS, ITGB3, NMNAT1* and *PLCZ1*. Gao *et al*. have found that von Hippel-Lindau Tumor Suppressor (*VHL*) was directly binding to the promoter of *ALDH2* to regulate the transcriptional activity of Hepatocyte Nuclear Factor 4 Alpha (*HNF4A*) in clear-cell renal cell carcinomas (38). Loss of *HNF4A* binding activity was often observed in renal cell carcinogenesis (39).

Germline alteration of *BRCA1, BRCA2* and *PMS2* were also detected in this study. Germline *BRCA1* and/or *BRCA2* deleterious mutation caused hereditary breast and ovarian cancer as well as other types of familiar cancer syndrome (40). Moreover, cancer caused by *BRCA1* mutation was sensitive to PARP1 inhibitors, such as olaparib and talazoparib. Recent clinical trials showed that PARP1 inhibitor prolonged duration of survival in patients with metastatic breast cancer with pathogenic *BRCA1* and/or *BRCA2* mutations (41, 42). We found a deleterious mutation of *PMS2*, one of mismatch repair (MMR) genes associated with Lynch syndrome (43). With regard to immune checkpoint blockade had more clinical benefit in MMR deficient cancers compared to MMR proficient cancers, anti-PD-1 antibody wound be considered as a therapeutic option in PRCC2 with *PMS2* mutation.

Recent genetic study using targeted deep sequencing determined

that approximately 20% of advanced renal cell carcinomas had a germline mutation even though almost all cases were sporadic rather than hereditary cancer. That study found *BRCA1*, *BRCA2,* and *CHEK2* germline mutations and suggested that half of germline mutations could be potential targets for direct systemic treatment (44). Therefore, these germline mutations are potential therapeutic targets in advanced PRCC2.

Somatic mutations in PRCC2 also indicated disease prognosis. One patient with metastatic disease harboring *SETD2* and *PBRM1* somatic mutations had overall survival of about 5 years despite having stage IV PRCC2. His disease showed a durable response to axitinib and had a relatively good prognosis. Both *SETD2* and *PBRM1* were SWI/SNF complex genes associated with chromatin remodeling. In clear cell renal cell carcinoma, *SETD2* was associated to poor prognosis while *PBRM1* had no impact on patient's survival or also indicated poor prognosis (45, 46). In this case, we treated PRCC2 as clear cell RCC with axitinib and he might be have favorable treatment outcome.

Our results indicate the role of genetic alterations in precision systemic treatment of PRCC2. *FH* alterations were found in not only HLRCC, but also in sporadic PRCC2. Sporadic PRCC2 with somatic *FH* frameshift deletion had similar clinical outcome to HLRCC. In addition, genetic alterations of *PBRM1* and *SETD2* had a predictive

role of PRCC2 prognosis.

In this genetic study, we successfully applied genetic information to patient treatment and prolonged survival. Therefore, genome sequencing should be performed to identify candidates for targeted therapy in PRCC2, a genetically heterogeneous disease.

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초 록

서론: 유두 신장암 아형2 (PRCC2)는 전신 치료에 잘 반응하지 않고, 투명세포 신장암 (ccRCC)과 비교하여 현저히 예후가 좋지 않다. 우리는 이전 연구에서 PRCC2는 높은 PBRM1 발현을 보였으며 예후가 좋지 않다고 보고하였고, 이전의 유전자 연구는 PRCC2의 유전자 변경이 생식선 또는 체세포 돌연변이와 상관없이 이질적임을 보여 주었다. 본 연구에서는 유전자 정보를 기반으로 PRCC2의 정밀 치료를 수행하고자 하였다.

방법: 우리는 유두 신장암 아형2의 종양조직과 같이 정상조직의 전체 엑솜 시퀀싱 및 게놈 시퀀싱을 수행했다. 이러한 시퀀싱 데이터를 기반으로, 전이성 PRCC2 환자에서 정밀 맞춤치료를 시행하였다.

결과: 4 명의 환자가 PRCC2의 치료 수술을 받았으며 3 명의 환자는 전이성 PRCC2로 진단되었다. 모든 PRCC2는 자신의 드라이버 돌연변이를 가졌고, 모두 이질적이었다. 전이성 질환을 가진 3 명의 환자 중 2 명은 푸마 레이트 히드라 타제 (FH) 생식선 돌연변이를 가졌고, 생식선 FH 돌연변이를 갖는 한 명의 환자는 유전성 평활근종증 신장암으로 진단되었다. 그는 혈관내피생성인자A를 억제하는 베바시주맙(bevacizumab) 및 표피세포성장인자 수용체 억제제인 엘로티닙(erlotinib)으로

치료받았고, 내구성이 있는 반응을 보였다. 생식선 FH 돌연변이를 갖는 다른 전이성 PRCC2 환자는 추가적인 체세포 FH 돌연변이를 가졌고 신생혈관생성을 억제하고, 선택적 다발성 수용체 억제제인 파조파닙(pazopanib)으로 효과적인 치료를 받을 수 있었다. 체세포 PBRM1 및 SETD2 돌연변이를 갖는 다른 전이성 PRCC2 환자는 악시티닙(axitinib) 치료로 5 년 이상의 전체 생존율을 가졌다.

결론: 본 연구에서 우리는 유전자 정보를 기반으로 맞춤치료를 시행하였다. 유전자분석은 유전적으로 이질적이고, 기존 치료에 잘 반응하지 않는 질병인 PRCC2의 표적 치료 약제를 선택하는데 도움이 될 수 있을 것으로 생각된다.

주요어: 유두 신장암 아형2; 체계적 분석; 차세대 유전체 시퀀싱; 맞춤치료

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